doi:10.1093/scan/nsr051 SCAN (2012) 7, 727–737

The balance between feeling and knowing: affective and cognitive empathy are reflected in the brain's intrinsic functional dynamics

Christine L. Cox,[1,*] Lucina Q. Uddin,[2,*] Adriana Di Martino,[1] F. Xavier Castellanos,[1,3] Michael P. Milham,[1,3] and Clare Kelly[1]

[1]Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience at the New York University Child Study Center, NYU Langone Medical Center, New York, NY, USA, [2]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA, and [3]Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, USA

Affective empathy (AE) is distinguished clinically and neurally from cognitive empathy (CE). While AE is selectively disrupted in psychopathy, autism is associated with deficits in CE. Despite such dissociations, AE and CE together contribute to normal human empathic experience. A dimensional measure of individual differences in AE 'relative to' CE captures this interaction and may reveal brain–behavior relationships beyond those detectable with AE and CE separately. Using resting-state fMRI and measures of empathy in healthy adults, we show that relative empathic ability (REA) is reflected in the brain's intrinsic functional dynamics. Dominance of AE was associated with stronger functional connectivity among social–emotional regions (ventral anterior insula, orbitofrontal cortex, amygdala, perigenual anterior cingulate). Dominance of CE was related to stronger connectivity among areas implicated in interoception, autonomic monitoring and social–cognitive processing (brainstem, superior temporal sulcus, ventral anterior insula). These patterns were distinct from those observed with AE and CE separately. Finally, REA and the strength of several functional connections were associated with symptoms of psychopathology. These findings suggest that REA provides a dimensional index of empathic function and pathological tendencies in healthy adults, which are reflected in the intrinsic functional dynamics of neural systems associated with social and emotional cognition.

Keywords: affective empathy; cognitive empathy; fMRI; resting-state functional connectivity; social cognition

INTRODUCTION

Empathy, the ability to understand and identify with the feelings or emotional states of others, is multidimensional, comprising both affective and cognitive components (Deutsch and Madle, 1975). Although the literature has yet to agree on a precise definition of these constructs, a consensus has emerged that views affective empathy (AE) as the ability to share the emotional experiences of others, i.e. a visceral reaction to their affective states; while cognitive empathy (CE) denotes the ability to take the mental perspective of others, allowing one to make inferences about their mental or emotional states (Shamay-Tsoory, 2011). AE and CE are dissociably disrupted in psychiatric illness. Psychopathy, schizophrenia, depersonalization and narcissism are characterized by deficits in AE but not CE (Blair, 2005; Lawrence *et al.*, 2007; Shamay-Tsoory *et al.*, 2007; Jones *et al.*, 2010; Ritter *et al.*, 2011). Conversely, autism, bipolar disorder and borderline traits are associated with impairment in CE but not AE (Dziobek *et al.*, 2008; Shamay-Tsoory *et al.*, 2009a; Harari *et al.*, 2010). Concomitant deficits in both domains (Lough *et al.*, 2006), along with abnormal patterns of intrinsic functional connectivity (Zhou *et al.*, 2010), occur in fronto-temporal dementia. Even among non-clinical populations, the balance between AE and CE varies from one individual to the next, uniquely defining the human empathic experience for each person (Kerem *et al.*, 2001).

Brain lesion studies provide insight into the neurobiology of dissociable AE and CE deficits. For example, bilateral amygdala damage (Hurlemann *et al.*, 2010) and localized damage to the inferior frontal cortex/anterior insula selectively disrupt AE (Shamay-Tsoory *et al.*, 2009b). Conversely, CE is selectively disrupted with medial prefrontal cortex lesions (Shamay-Tsoory *et al.*, 2009b), as well as normal aging (Bailey *et al.*, 2008). Interestingly, oxytocin, a peptide implicated in prosocial and parenting behaviors (Skuse and Gallagher, 2011), enhances AE but not CE (Hurlemann *et al.*, 2010), further highlighting a biological basis for dissociable empathic domains.

Received 18 March 2011; Accepted 26 July 2011
Advance Access publication 5 September 2011

The authors thank Dr Xi-Nian Zuo for assistance with fALFF analyses, and all participants for their time and cooperation. This work was supported by the National Institute on Drug Abuse (2T32DA007254-16A2 for C.L.C., R03DA024775 to C.K., and R01DA016979 to F.X.C.); the National Institute of Mental Health (K01MH092288 to L.Q.U., K23MH087770 to A.D.M., and R01MH083246 and R01MH081218 to F.X.C. and M.P.M.); the Leon Levy Foundation (A.D.M. and M.P.M.); the Stavros Niarchos Foundation; and an endowment from Phyllis Green and Randolph Cowen.

Correspondence should be addressed to Clare Kelly, Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience at the NYU Child Study Center, 215 Lexington Ave. 14th Floor, New York, NY 10016, USA. E-mail: Clare.Kelly@nyumc.org

*These authors contributed equally to this work.

Neuroimaging studies typically highlight brain regions implicated in empathy more generally (Carr *et al.*, 2003; Zaki *et al.*, 2009; Decety, 2010; Fan *et al.*, 2011) often due to a lack of agreement regarding the terminology and cognitive constructs employed [e.g. empathy for pain (Decety, 2010), Theory of Mind (ToM) (Saxe, 2006), automatic *vs* controlled empathy (Fan *et al.*, 2011)]. Nonetheless, several studies point to distinctions in the neural correlates of AE and CE. During a social–emotional task, activation in inferior frontal gyrus, supramarginal gyrus and superior temporal sulcus was related to CE, while activation in precentral gyrus was associated with AE (Hooker *et al.*, 2010). In addition, AE as opposed to CE tasks preferentially recruit the insula, brainstem, inferior parietal lobule, thalamus (Nummenmaa *et al.*, 2008) and medial orbitofrontal cortex (OFC) (Hynes *et al.*, 2006).

Here, we report a novel approach to examining the neural correlates of empathy that: (i) demonstrates the utility of examining individual differences in the balance between AE and CE rather than the two domains individually and (ii) overcomes the lack of agreement regarding appropriate task probes by using resting state functional magnetic resonance imaging (R-fMRI). R-fMRI approaches characterize the intrinsic functional dynamics and connectivity of brain networks while avoiding some of the constraints of task-based approaches (Biswal *et al.*, 1995; Greicius *et al.*, 2003; Fox and Raichle, 2007; Cole *et al.*, 2010). Networks identified using resting-state functional connectivity (RSFC) methods demonstrate strong correspondence with networks of coactivated brain regions detected across myriad task paradigms, suggesting that they constitute intrinsic representations of the brain's functional repertoire (Toro *et al.*, 2008; Smith *et al.*, 2009). Recently, R-fMRI approaches have been applied to the study of brain–behavior relationships, demonstrating robust relationships between individual differences in measures of personality traits and behavior and individual differences in RSFC (Andrews-Hanna *et al.*, 2007; Di Martino *et al.*, 2009; Cox *et al.*, 2010; Hoptman *et al.*, 2010a). Here, we applied this brain–behavior approach to examine the extent to which individual differences in AE and CE are reflected in the brain's intrinsic functional dynamics, using R-fMRI data collected from 38 healthy adults.

We used the Interpersonal Reactivity Index (IRI), a widely used self-report, multidimensional measure of dispositional empathy (Davis, 1980, 1983). More specifically, we used the Empathic Concern (EC) and Perspective Taking (PT) subscales of the IRI to measure AE and CE, respectively (Davis, 1983; Rankin *et al.*, 2006). The EC subscale reflects one's affective reaction to others' emotions, while the PT subscale denotes the tendency to take the mental perspective of others (Davis, 1980, 1983). Several studies support the construct validity of these subscales as indices of AE and CE. Specifically, EC scores are correlated with measures of emotionality, concern for others and affective empathy. PT scores, on the other hand, are related to measures of social competence, other-oriented sensitivity and cognitive empathy (Davis, 1983; Davis *et al.*, 1994; de Corte *et al.*, 2007).

Rather than examining AE and CE individually, we devised an IRI-based measure called relative empathic ability (REA) to assess individual differences in the balance between AE and CE. REA is the difference between the EC and PT subscales, and as such, reflects the dominance of one type of empathic ability over the other, rather than absolute empathic ability. Our focus on individual differences in the 'discrepancy' between AE and CE was motivated by studies demonstrating that a number of psychiatric disorders are characterized by a dissociation between abilities in one domain relative to the other (i.e. impaired CE but not AE and vice versa) (Blair, 2005; Lawrence *et al.*, 2007; Shamay-Tsoory *et al.*, 2007, 2009a; Dziobek *et al.*, 2008; Harari *et al.*, 2010; Jones *et al.*, 2010; Ritter *et al.*, 2011). Accordingly, in addition to exhibiting brain–behavior relationships related to REA, we predicted that those individuals exhibiting the greatest discrepancy between AE and CE would also exhibit the highest levels of pathological traits.

Prior studies have implicated numerous brain regions in empathic processing (Carr *et al.*, 2003; Zaki *et al.*, 2009; Decety, 2010; Fan *et al.*, 2011), making *a priori* selection of a comprehensive set of regions of interest (ROIs) for RSFC analyses difficult. Thus, similar to prior work (Lui *et al.*, 2010; Kelly *et al.*, 2011), we used an unbiased, data-driven method to define relevant ROIs for subsequent seed-based RSFC analyses. Specifically, we examined the relationship between REA scores and a voxel-wise frequency-domain measure of BOLD signal dynamics, fractional amplitude of low-frequency fluctuations (fALFF) (Zou *et al.*, 2008). fALFF quantifies the power of low-frequency (0.01–0.1 Hz) BOLD fluctuations relative to the total power across all measurable frequencies in the BOLD time series. As opposed to functional connectivity, a measure of the 'relationships' between patterns of intrinsic activity across different brain regions, fALFF is a 'regional' measure, reflecting the temporal dynamics of the BOLD signal (i.e. signal variability) at each voxel in the brain. It is analogous to time-domain measures of band-passed BOLD signal standard deviation (Kannurpatti and Biswal, 2008; Garrett *et al.*, 2010). fALFF is strongest in gray matter and has been shown to be highly reliable across both short and long test–retest intervals (Zuo *et al.*, 2010). Abnormal fALFF has been observed in neurological psychiatric disorders (Hoptman *et al.*, 2010b; Han *et al.*, 2011) and is also associated with functional brain activity in task-based fMRI paradigms (Zhang and Li, 2010). Importantly for the current study, fALFF is associated with individual differences in behavior (Mennes *et al.*, 2011) and personality traits (Kunisato *et al.*, 2011a, b). In the current study, fALFF analyses identified brain regions whose intrinsic dynamics were associated with individual differences in REA. Areas exhibiting maximal REA–fALFF relationships

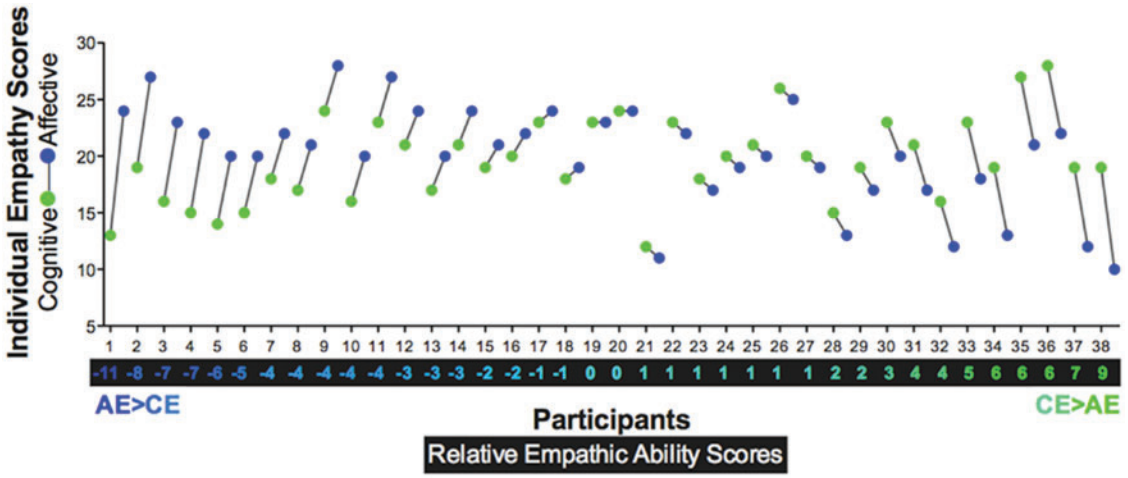

Fig. 1 Each participant's ($n = 38$) absolute affective empathy (AE; blue) and cognitive empathy (CE; green) scores are plotted, with their relative empathy score (REA) (CE minus AE; gradient from blue to green) displayed below the *x*-axis. Negative scores indicate a dominance of affective empathy (AE > CE), and positive scores indicate a dominance of cognitive (CE > AE).

were then used as ROIs for subsequent analyses examining the relationship between REA scores and voxel-wise whole-brain RSFC.

Finally, since deficits in empathy, particularly discrepancies between AE and CE, have been reported across multiple disorders with distinct psychopathologies, we investigated the correlation between REA and its associated brain–behavior relationships and measures of a broad range of symptoms of psychopathology (e.g. interpersonal sensitivity, depression, anxiety, paranoia, psychoticism, hostility). Since empathic deficits have also been associated with more specific pathological traits, such as increased impulsivity, aggression and antisocial behavior (Miller and Eisenberg, 1988; Reniers *et al.*, 2011) as well as autistic traits (Dziobek *et al.*, 2008), we also examined correlations with measures of impulsivity, aggression and autistic traits. All of these analyses were repeated for AE and CE scores separately to determine whether unique information is provided by REA.

MATERIALS AND METHODS

Participants

Thirty-eight healthy adults (20 female; mean age = 30.0, s.d. = 8.5 years) with no history of neurological or psychiatric illness (confirmed by psychiatric interview) were selected from a larger sample of healthy adults participating in ongoing studies conducted by our group. Selection was based on participants having completed the IRI questionnaire and at least one motion-free resting-state scan. The study was approved by the NYU institutional review boards, and prior written informed consent was obtained from all participants according to the Declaration of Helsinki. Data from these participants (publicly available for download at http://fcon_1000.projects.nitrc.org) have been reported in prior published studies (Di Martino *et al.*, 2009; Shehzad *et al.*, 2009; Zuo *et al.*, 2010).

REA

Participants completed the IRI, a self-report, well validated, multidimensional measure of empathy (Davis, 1980, 1983), comprising four subscales: two indexing affective empathy (Empathic Concern, Personal Distress), and two indexing cognitive empathy (Perspective Taking, Fantasy). Several studies have reported concerns regarding the reliability and validity of the Personal Distress and Fantasy subscales (Baron-Cohen and Wheelwright, 2004; Rankin *et al.*, 2006). Accordingly, and consistent with prior studies (Rankin *et al.*, 2006; Shane *et al.*, 2009; Ritter *et al.*, 2011), we did not include the Personal Distress or Fantasy subscales in our analyses, but instead relied on the EC and PT subscales as demonstrably valid measures of AE and CE.

We used the difference between PT and EC subscales (PT minus EC) as an index of an individual's REA (CE minus AE). Negative difference scores indicated a dominance of AE and positive scores indicated a dominance of CE (Figure 1). For consistency with previous work (Harari *et al.*, 2010), we focused on the difference between these two subscales. One possible concern that may arise with the use of a difference measure is that it may be driven by an individual's total empathy (CE + AE). We found no evidence of such a correlation between REA and total empathy across subjects [$r(36) = -0.18$, $P = 0.29$]. We considered the alternative approach of using a ratio measure (e.g. CE/AE), though found the two measures to be nearly identical [$r(36) = 0.96$, $P < 0.0001$]. Given concerns about the reliability of ratio measures, especially when the individual components are non-independent (Arndt *et al.*, 1991), we opted to use a difference score. Though not a concern in the current

study, this may be particularly relevant when investigating REA in populations with more extreme high or low CE and AE scores, as found in various psychopathologies.

REA, as a relative measure, reflects the dominance of one type of empathic ability over the other (e.g. AE > CE). As such, REA does not reflect absolute levels of empathic ability; an individual can have high scores (or low scores) on both AE and CE scales, resulting in an REA score of zero and indicating no discrepancy between AE and CE abilities. Although certain disorders have been associated with deficits in both AE and CE (i.e. frontotemporal dementia; Lough *et al.*, 2006), the majority of reported empathic deficits across various neuropsychiatric disorders have been characterized by discrepancy between the two domains. This discrepancy can be observed as a deficit (e.g. impaired AE but not CE in schizophrenia; Shamay-Tsoory *et al.*, 2007) or as disproportionately higher scores (e.g. increased AE but not CE in borderline personality disorder; Harari *et al.*, 2010). We therefore focused on REA in order to capture brain–behavior relationships associated with this discrepancy in a healthy population. As REA does not capture brain–behavior relationships associated with absolute levels of empathic ability, we also include supplemental analyses investigating AE and CE separately (see below) to fully characterize these relationships.

Data acquisition

Images were collected on a Siemens Allegra 3-T scanner. An R-fMRI scan (197 echo planar imaging (EPI) volumes; repetition time (TR) = 2000 ms; echo time (TE) = 25 ms; flip angle = 90°; 39 slices; field of view (FOV) = 192 mm; voxel size = 3 × 3 × 3 mm) and an magnetization prepared rapid gradient echo (MPRAGE) anatomical image (TR = 2500 ms; TE = 4.35 ms; inversion time (TI) = 900 ms; flip angle = 8°; 176 slices; FOV = 256 mm) were acquired. For 33 participants, the rest scan from their first scanning session was used; for the remaining 5, the scan from a second session was included (due to excessive motion in the first scan). Scan session (1 or 2) was modeled as a nuisance covariate in all analyses.

Preprocessing

Data processing was performed using Analysis of Functional NeuroImages (AFNI; http://afni.nimh.nih.gov/afni) and FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk). Image preprocessing comprised slice time correction; 3D motion correction; despiking (removal of extreme time series outliers); spatial smoothing (FWHM: 6 mm); mean-based intensity normalization of all volumes by the same factor and linear and quadratic detrending. Temporal filtering was not used for fALFF analyses (see below). Temporal bandpass filtering (0.009–0.1 Hz) was implemented for RSFC analyses (also see below). Linear registration of the MPRAGE anatomical image to the MNI152 template (FSL *FLIRT*) (Jenkinson *et al.*, 2002) was refined using *FNIRT* nonlinear registration (Andersson *et al.*, 2007).

For RSFC analyses only, we regressed each participant's 4D pre-processed volume on nine nuisance signals (white matter, CSF, the global signal and six motion parameters). Each participant's resultant 4D residuals volume was spatially normalized by applying the transformation to MNI152 standard space (resolution = 2 mm^3).

fALFF and REA

For each participant, we calculated fALFF (Zuo *et al.*, 2010; Mennes *et al.*, 2011), a voxel-wise measure of local BOLD signal dynamics that emphasizes potentially meaningful low-frequency fluctuations over higher frequency signals that likely reflect physiologic noise and pulsatile motion. fALFF is a periodogram-based measure, calculated as the total power within the low frequency range (0.01–0.1 Hz), divided by the total power detectable across the periodogram (maximum frequency = 0.25 Hz). fALFF values were transformed into *Z*-scores prior to group analyses (Zuo *et al.*, 2010).

Group-level analyses were performed using a mixed-effects model (FSL *flameo*; ordinary least squares) with REA scores as a covariate of interest and three nuisance covariates (age, sex, scan session). This analysis produced a Z-statistic map of voxels in which fALFF exhibited significant variation in association with REA. Cluster-based correction for multiple comparisons was performed using Gaussian random field theory ($Z > 2.3$; cluster significance: $P < 0.05$ corrected). Peak locations (i.e. local maxima of the correlation between fALFF and REA, detected with *3dmaxima*; minimum 20 mm apart) were used to define seed regions for RSFC analyses.

RSFC and REA

Group-level fALFF–REA analyses yielded 10 peaks, the coordinates of which formed the centers of spherical seed ROIs

Table 1 Peak coordinates from brain regions with significant fALFF–REA relationships

Region	Hemisphere	Peak coordinates			fALFF–REA relationship
		x	*y*	*z*	
Orbitofrontal cortex	R	24	8	−20	AE > CE
Amygdala	L	−20	0	−22	AE > CE
Anterior insula	L	−42	14	−12	AE > CE
Anterior insula/temporal pole	R	44	10	−14	AE > CE
Mid-posterior insula	R	44	−8	0	AE > CE
Parahippocampal gyrus	L	−16	−32	−18	AE > CE
Brainstem (pons)	L	−2	−34	−24	AE > CE
Brainstem (medulla)	Bilat	0	−34	−44	AE > CE
Thalamus	L	−20	−22	12	CE > AE
Putamen	L	−24	10	8	CE > AE

Coordinates are reported in MNI152 space.
L, left; R, right; Bilat, bilateral.

(radius = 4 mm) (Table 1; Supplementary Figure S1). For each participant, and each ROI, we extracted the mean time series across voxels falling within that ROI and performed a correlation analysis using AFNI (*3dfim+*). Resultant correlation maps were transformed to standard space. Scripts containing a similar sequence of processing commands are available via the 1000 Functional Connectomes Project (Biswal *et al.*, 2010) (http://www.nitrc.org/projects/fcon_1000).

Group-level analyses for each seed ROI were performed using a mixed-effects model implemented in FSL *flameo* (ordinary least squares) that included REA scores as a covariate of interest and three nuisance covariates (age, sex, scan session). This group-level analysis produced thresholded *Z*-statistic maps of voxels whose RSFC with the seed ROI exhibited significant variation in association with REA. Cluster-based statistical correction for multiple comparisons was performed using Gaussian random field theory ($Z > 2.3$; cluster significance: $P < 0.05$ corrected).

fALFF and RSFC with AE and CE individually

Although REA and its neural correlates were our primary focus, additional fALFF and RSFC analyses were also performed including the separate empathy subscales (i.e. AE and CE) as covariates. Methods for fALFF–AE and fALFF–CE analyses were identical to those for fALFF–REA, except that demeaned AE scores and demeaned CE scores were entered as covariates in separate group-level models. Three spherical seed ROIs (radius = 4 mm) were defined centered on the peak voxel coordinates from the fALFF–AE and fALFF–CE group analyses (Supplementary Table S1 and Supplementary Figure S2). Methods for RSFC–AE and RSFC–CE analyses were identical to those for RSFC–REA, except that demeaned AE scores and demeaned CE scores were entered as covariates in separate group-level models.

REA, pathological traits and intrinsic brain dynamics

As part of a comprehensive clinical and cognitive evaluation carried out on all participants, a battery of questionnaire measures of behavioral and psychopathological traits was collected. Since deficits in empathy, particularly discrepancies between AE and CE, have been reported for multiple psychiatric disorders (e.g. psychopathy, depersonalization, narcissism, autism, schizophrenia, bipolar disorder and borderline traits), we investigated the relationships between REA and its associated functional connectivity patterns and measures of relevant pathological traits collected as part of the questionnaire battery. Specifically, we computed Pearson correlations between REA scores and scores on the Social Responsiveness Scale-Adult Version (SRS-A; available for 18 participants), an informant measure of autistic traits (Constantino, 2002); the Barratt Impulsiveness Scale (BIS; available for 37 participants), a multidimensional self-report measure of general impulsiveness (Patton *et al.*, 1995); and the Buss–Perry Aggression Questionnaire (BPAQ; available for 34 participants), a widely used self-report measure of trait aggression (Buss and Perry, 1992). Due to a non-normal distribution of scores, non-parametric Spearman correlation analyses were carried out between REA and the Symptom Checklist-90-Revised (SCL-90-R; available for all 38 participants), a self-report measure of a broad range of psychological problems and symptoms of psychopathology (Derogatis, 1994). To account for the number of tests (SRS-A Total score, BIS Total score, BPAQ Total and four subscale scores, SCL-90 10 subscale scores), a Bonferroni correction ($P < 0.05/17$ tests $= 0.003$) was applied to all analyses. Analyses were repeated for each empathy subscale (AE and CE) separately to determine whether REA provided information beyond the two domains individually.

We further determined whether pathological traits exhibiting significant correlations with REA also exhibited similar brain–behavior relationships. fALFF and RSFC values were extracted for clusters exhibiting significant relationships with REA, then correlated with trait measures that exhibited significant relationships with REA.

RESULTS

AE, CE and REA

Participants reported absolute AE and CE scores similar to previously reported norms (Davis, 1980) [mean AE = 20.1 (s.d. 4.5); mean CE = 19.6 (s.d. 3.8)], which were moderately correlated [$r\ (36) = 0.41$, $P < 0.01$]. REA scores (CE minus AE) ranged from −11 to +8, reflecting a distribution of dominance in AE [−] or CE [+] across our participants (Figure 1).

There were no gender differences in absolute or relative empathy scores; nonetheless, sex (as well as age) was included as a covariate in all group-level brain–behavior analyses.

fALFF and REA

We employed an unbiased, data-driven method to identify candidate regions for subsequent investigations of the relationship between intrinsic functional connectivity and REA. As a first step, we identified brain areas whose intrinsic functional dynamics, as measured by fALFF (Zou *et al.*, 2008, 2010), were associated with individual differences in REA. This yielded a map of regions in which fALFF varied as a function of individuals' self-reported relative strength in AE or CE.

We observed fALFF–REA brain–behavior relationships in bilateral insula, temporal poles, OFC, brainstem and cerebellum, and in left putamen, thalamus, amygdala and parahippocampal gyrus. Ten peaks within this map (i.e. local maxima of significant REA–fALFF correlations, >20 mm apart) were identified; their coordinates formed the centers of seed ROIs for RSFC analyses (Table 1 and Supplementary Figure S1). Notably, these regions were distinct from those in which fALFF was related to AE or CE individually

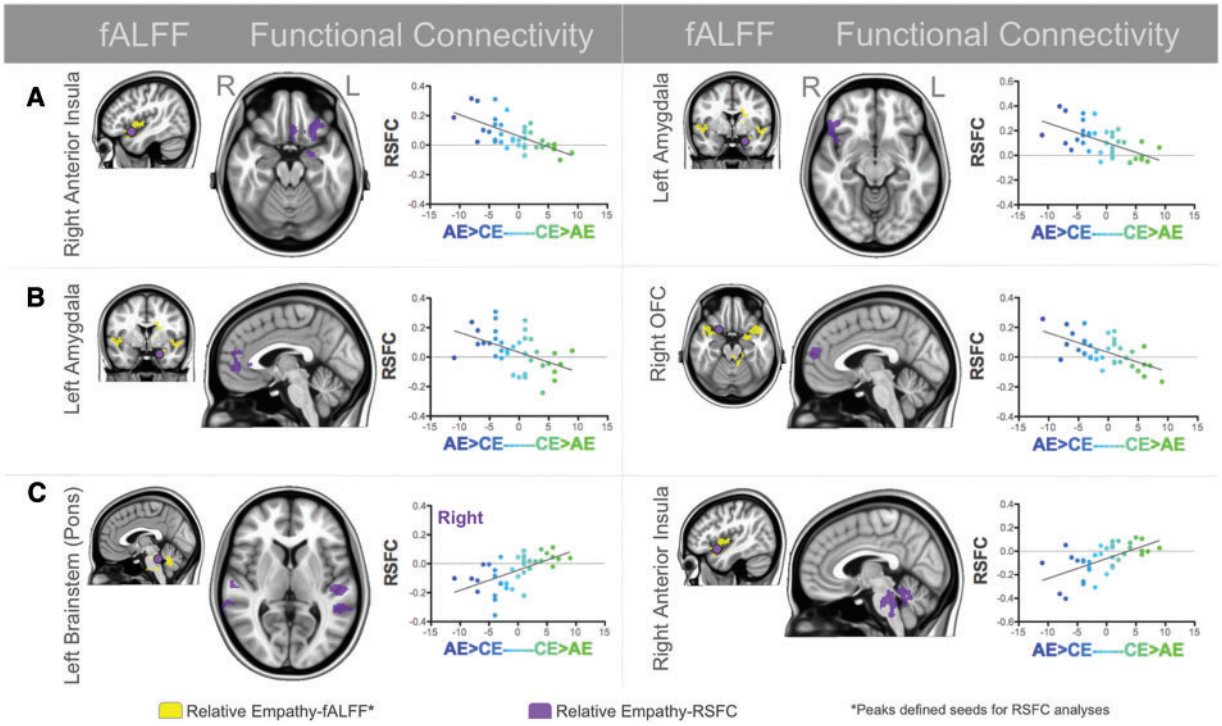

Fig. 2 Examples of the three patterns of the RSFC–REA brain–behavior relationships. Brains with yellow clusters indicate significant fALFF–REA relationships, the peaks of which defined seed regions for RSFC analyses, identified with purple dots. Brains with purple clusters represent significant RSFC-REA relationships with the seed region. (**A**) Dominance of AE was associated with stronger positive RSFC, dominance of CE with weaker positive RSFC; observed between the right ventral anterior insula seed and left OFC/subcallosal cortex/amygdala (left column), and the left amygdala seed and right OFC/temporal pole/ventral anterior insula (right column). (**B**) Dominance of AE was associated with stronger positive RSFC, dominance of CE with stronger negative RSFC; observed between the left amygdala seed and bilateral perigenual ACC (left column), and the right OFC seed and bilateral paracingulate gyrus (right column). (**C**) Dominance of CE was associated with stronger positive RSFC, dominance of AE with stronger negative RSFC; observed between the left brainstem (pons) seed and bilateral superior temporal gyri/sulci (left column), and the right ventral anterior insula seed and bilateral brainstem/cerebellum (right column). All results were significant at $Z > 2.3$, cluster significance: $P < 0.05$ corrected for multiple comparisons using Gaussian random field theory. Brains are presented in radiological orientation (right = left).

(Supplementary Table S1 and Supplementary Figure S2), suggesting that REA provides unique information about the relationships between individual differences in empathic abilities and intrinsic functional brain dynamics.

RSFC and REA

Next, we conducted RSFC analyses to identify networks whose intrinsic connectivity was modulated by individual differences in REA. Three overall patterns of RSFC–REA brain–behavior relationships were observed, as illustrated below with specific examples of each. Full results for all seed ROIs are detailed in Supplementary Table S2.

Pattern A

Dominance of AE was associated with stronger positive within-network RSFC, while dominance of CE was associated with weaker positive within-network RSFC. This pattern was observed for RSFC between the right ventral anterior insula seed and left OFC, extending to subcallosal cortex and amygdala (Figure 2A, left column), and between the left amygdala seed and right OFC, extending to the temporal pole and ventral anterior insula, including the location of the ventral anterior insula seed (Figure 2A, right column).

Pattern B

Dominance of AE was associated with stronger positive within-network RSFC, similar to Pattern A; however, dominance of CE was associated with stronger negative RSFC (i.e. greater functional differentiation, or separation among regions or networks). For example, this pattern was observed for the relationship between the left amygdala seed and bilateral perigenual ACC (Figure 2B, left column), and between the right OFC seed and bilateral paracingulate gyrus, just rostral to perigenual ACC (Figure 2B, right column). Patterns A and B suggest that AE dominance is associated with stronger intrinsic functional connectivity between brain regions involved in social and emotional processing.

Pattern C

The converse of Pattern B, this pattern revealed that dominance of CE was associated with stronger positive within-network RSFC, while dominance of AE was associated with stronger negative RSFC (greater functional differentiation). For example, this pattern was observed for the relationship between the left brainstem (pons) seed and bilateral superior temporal gyri/sulci (STG/STS) (Figure 2C,

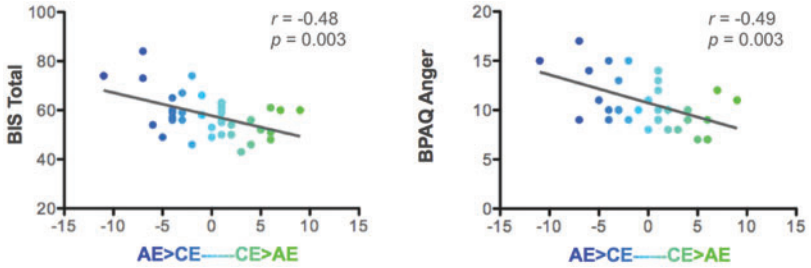

Fig. 3 REA scores were significantly negatively correlated with Barratt Impulsiveness Scale (BIS) total scores (left graph) and Buss-Perry Aggression Questionnaire (BPAQ) Anger subscale scores (right graph). Relative weakness in CE and dominance of AE was associated with higher levels of impulsivity and anger-related aggression. All tests were thresholded using a Bonferroni correction for multiple comparisons ($P < 0.05/17 = 0.003$).

left column), and between the right ventral anterior insula seed and bilateral brainstem (including the location of the pons seed) extending to the cerebellum (Figure 2C, right column). This pattern suggests that dominance of CE is associated with stronger RSFC between brain regions involved in interoception, autonomic monitoring and mentalizing.

Again, these relationships were distinct from those detected for AE or CE separately (Supplementary Table S3), further suggesting that REA provides unique information about the relationship between empathic ability and the intrinsic functional connectivity of the brain.

There were no gender differences in the correlations between REA and RSFC for any of the regions examined.

Pathological traits, REA and intrinsic functional brain dynamics

Discrepancy between AE and CE (i.e. deficits in one but not the other) has been associated with a range of psychiatric conditions. We hypothesized that REA, as a measure of the divergence between AE and CE scores, would be sensitive to symptoms of psychopathology in a non-clinical population. We also examined whether RSFC between brain regions significantly associated with REA was related to measures of pathological traits in these individuals.

The BIS, a self-report measure of general impulsiveness, was significantly negatively correlated with REA [$r(35) = -0.48$, $P = 0.003$] (Figure 3). Relative weakness in CE (i.e. higher AE relative to CE) was associated with higher impulsivity. In addition, the Anger subscale of the BPAQ, a self-report measure of trait aggression, was significantly negatively correlated with REA [$r(32) = -0.49$, $P = 0.003$] (Figure 3). Relative weakness in CE was associated with higher anger-related aggression. Although there were trends suggesting a negative relationship with CE alone, neither impulsivity nor anger scores were significantly correlated with AE or CE scores individually at a threshold of $P < 0.003$, Bonferroni corrected for the number of tests [BIS-AE: $r(35) = 0.13$, $P = 0.45$; BIS-CE: $r(35) = -0.40$, $P = 0.014$; BPAQ-AE: $r(32) = 0.20$, $P = 0.26$; BPAQ-CE: $r(32) = -0.35$, $P = 0.04$]. This suggests that REA may be a sensitive indicator of pathological traits in a population of healthy individuals, capturing information not provided by interrogating each dimension alone.

In addition, impulsivity and anger scores were significantly correlated with fALFF in and RSFC between several regions identified in the REA analyses (Supplementary Table S4). Supplementary Figure S3 illustrates several of these significant relationships. RSFC between the right anterior insula and left subcallosal cortex–OFC–amygdala was significantly correlated with both BIS and BPAQ scores. Stronger positive, within-network RSFC between these regions was associated with higher levels of impulsivity and anger. A similar pattern was observed between the right OFC and paracingulate gyrus, except only BPAQ scores were significant in this case. Stronger positive RSFC between these brain regions, which have been implicated in social and emotional processing, was related to (i) relatively lower CE in the context of relatively higher AE, (ii) impulsivity and (iii) anger-related aggression.

A different pattern was observed for RSFC between the right anterior insula and bilateral brainstem–cerebellum, which was negatively correlated with both BIS and BPAQ scores. Stronger negative RSFC, or greater functional differentiation between these areas, was associated with higher levels of impulsivity and anger. A similar relationship was observed with REA—stronger negative RSFC associated with relatively lower CE in the context of relatively higher AE. It is interesting that relative weakness in CE, higher impulsivity and higher anger were all associated with greater functional differentiation (i.e. stronger negative RSFC) between brain regions associated with the monitoring of one's internal bodily states and the experience of subjective emotion. We also observed a trend toward a negative relationship between impulsivity and RSFC between the left pons (associated with interoception and autonomic monitoring) and the right superior temporal gyrus (consistently implicated in mentalizing and social cognition). These results suggest that REA is not only sensitive to measures of pathological traits in healthy adults, but that the intrinsic functional dynamics of the brain that are associated with REA also show relationships with indicators of psychopathology.

In contrast, none of the subscales of the SCL-90-R, a self-report measure of a broad range of psychological problems and symptoms of psychopathology, were significantly correlated with REA (all P's > 0.003). In a subset of participants with available data, REA was not significantly correlated with the SRS-A, an informant measure of autistic traits continuously distributed in the general population [$r(16) = 0.23$, $P = 0.35$].

DISCUSSION

Human empathy comprises both affective and cognitive components. Here, in a sample of neurotypical adults, we showed that the balance between AE and CE (indexed by REA) was robustly related to the intrinsic dynamics within and functional connectivity between brain regions associated with social cognition, emotion processing, mentalizing, interoception and autonomic monitoring. These patterns were distinct from those of AE and CE separately. In addition, REA was significantly associated with measures of aggression and impulsivity, pathological traits previously related to empathic deficits (Miller and Eisenberg, 1988; Reniers *et al.*, 2011)—relationships again not observed with AE and CE alone. As demonstrated for individual differences in other personality and behavioral tendencies (Di Martino *et al.*, 2009; Kunisato *et al.*, 2011b), our results suggest that one's propensity toward affective or cognitive empathy is reflected in the intrinsic functional architecture of the brain.

Dominance of AE, and relative weakness in CE, was associated with stronger within-network functional connectivity in social–emotional networks, including a ventral anterior insula–OFC–subcallosal cortex–amygdala network, an amygdala–OFC–temporal pole-ventral anterior insula network, an amygdala–perigenual ACC network, and an OFC–paracingulate gyrus network (Figure 2A and B). Previous studies have implicated these brain areas in emotional and empathic processing. Singer *et al.* (2004) reported that a similar region of anterior insula (though with a slightly more dorsal peak) was activated both when experiencing pain and when observing a loved one in pain, which also correlated with self-reported AE. Reciprocal connections between the ACC, amygdala and ventromedial prefrontal cortex are proposed to underlie the ability to understand the emotional states of others (Decety, 2010). Specifically, the right anterior insula, along with OFC, is involved in the subjective awareness of feelings and emotions (Craig, 2002), emotional and empathic processing (Kurth *et al.*, 2010) and uniquely recruited during affective-perceptual (i.e. automatic, incidental) empathy tasks (Fan *et al.*, 2011).

Disruption to the normal function of and functional connections between these brain regions are observed in several disorders. Individuals with high functioning autism exhibit reduced RSFC between the right anterior insula and amygdala relative to typically developing controls (Ebisch *et al.*, 2011). Both psychopathic criminal offenders and patients with OFC lesions exhibit similar impairments in affective, but not cognitive, ToM tasks (Shamay-Tsoory *et al.*, 2010); and compromised functional integrity of the amygdala and OFC systems are thought to contribute to the development of psychopathy (Blair *et al.*, 2006). In addition, patients with schizophrenia were impaired in integrating the cognitive and affective components of ToM, which correlated with performance on a task indexing OFC functional integrity (Shur *et al.*, 2008).

In contrast, dominance of CE, and relative weakness in AE, was related to stronger within-network RSFC in social–cognitive and interoceptive networks, including a brainstem (pons)-STG/STS network and a ventral anterior insula–brainstem (pons and medulla)–cerebellum network (Figure 2C). The anterior insula, brainstem (specifically the pons) and cerebellum are active during both the experience of pain and observation of another person in pain (Singer *et al.*, 2004). As described above, the anterior insula is implicated in the experience of subjective emotion, thought to be based on the re-representation of the interoceptive state of one's body (primarily represented in the posterior insula), which in turn allows for the mental evaluation of emotions and feelings (Craig, 2002). The pons is involved in autonomic monitoring and interoception and is connected with other brain regions involved in these processes, such as the insula (Critchley, 2005). The role of the cerebellum in social cognition is increasingly appreciated; lesions to the posterior vermis and cerebellar hemispheres result in empathy and ToM deficits (Gerschcovich *et al.*, 2010). During an empathy-for-pain task, individuals with alexithymia (i.e. difficulty in recognizing and expressing one's own emotions) exhibit increased activation in the anterior insula and decreased activation in the pons and cerebellum compared to healthy controls (Moriguchi *et al.*, 2007).

Our results suggest that individuals with relatively high AE and relatively low CE show the greatest functional differentiation between these two networks (ventral anterior insula and pons-cerebellum), i.e. their intrinsic activity is anticorrelated, or out of phase. Conversely, individuals with relatively high CE and low AE show less functional differentiation and increased functional integration between the two networks. It is noteworthy that the same ventral anterior insula seed exhibited significant brain–behavior relationships with both a dominance of AE and of CE, but with distinct brain networks. Stronger AE was associated with stronger RSFC between the ventral anterior insula and social emotional regions (OFC–subcallosal cortex–amygdala), while stronger CE related to stronger RSFC with interoceptive and social cognitive regions (brainstem–cerebellum). These findings suggest that the intrinsic functional dynamics of the ventral anterior insula may be uniquely sensitive to individual differences in REA, likely reflecting its putative function as a critical interface between experiencing our own and understanding others' emotions (Keysers and Gazzola, 2007).

Stronger RSFC between the pons and bilateral STG/STS was also related to dominance of CE. These superior temporal cortical regions have been consistently implicated in ToM or mentalizing. The STS is a core region of the ToM network (Carrington and Bailey, 2009) and is part of a distributed network of regions involved in empathy (Decety, 2010). Activation in the STS has been specifically related to CE and not AE (Hooker *et al.*, 2010). Therefore, it is interesting that we observed stronger RSFC between the pons (involved in interoception) and the STS/STG in individuals with relatively stronger CE and weaker AE, while those with stronger AE and weaker CE showed more functional differentiation between these regions.

Notably, other measures of pathological traits exhibited significant relationships with REA, and with the intrinsic functional dynamics of brain regions associated with REA. Participants with relatively weaker CE and relatively stronger AE reported significantly greater impulsiveness and increased levels of anger-related aggression compared to those with relatively stronger CE and weaker AE, and these relationships were echoed in the brain. Neither AE nor CE scores alone were significantly related to these measures of psychopathology, suggesting that the relationship between these empathic dimensions is uniquely predictive of pathological traits. These results suggest that REA is not only sensitive to behavioral indices of psychopathology, but that these relationships are also reflected in the intrinsic functional architecture of the brain.

All of the brain–behavior relationships observed in the current study were unique to individual differences in relative empathic ability. Supplementary analyses (Supplementary Tables S1 and S3) using absolute AE and CE scores individually revealed brain–behavior relationships that were distinct from those observed with REA. In addition, REA proved to be a more sensitive index of psychopathology than either AE or CE alone. These results suggest that relative measures of empathy should be considered in neuroimaging, clinical and psychiatric studies, and that they can elucidate both healthy and pathological patterns of relationships that previously may have been obscured.

Although we observed predicted relationships between REA and the intrinsic functional architecture of the brain, further work is needed to conclusively link these associations to behavior. Unfortunately, we did not have objective behavioral data in these subjects (e.g. task performance) to supplement the self-report measures. However, the IRI is widely used, reliable and has good construct validity as a measure of empathic behavior (Davis, 1983). Finally, given consistent demonstrations of CE deficits in autism spectrum disorders and AE deficits in psychopathy, measuring autistic and/or psychopathic traits would have been of interest. Although we collected a measure of autistic traits continuously distributed in the general population (the SRS-A) from a subset of participants, we were limited by a relatively small sample size ($n = 18$) and did not observe any significant relationships with REA. Future studies will address these limitations with larger sample sizes and more varied measures of psychopathology, and will include clinical populations, such as individuals on the autism spectrum or those at risk for or exhibiting antisocial/psychopathic traits.

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online

Conflict of Interest

None declared.

REFERENCES

Andersson, J., Jenkinson, M., Smith, S. (2007). TR07JA2 : Non-linear registration, aka Spatial normalisation. *FMRIB Analysis Group Technical Reports.* http://www.fmrib.ox.ac.uk/analysis/techrep/.

Andrews-Hanna, J.R., Snyder, A.Z., Vincent, J.L., et al. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron*, *56*(5), 924–35.

Arndt, S., Cohen, G., Alliger, R.J., Swayze, V.W.II, Andreasen, N.C. (1991). Problems with ratio and proportion measures of imaged cerebral structures. *Psychiatry Research*, *40*(1), 79–89.

Bailey, P.E., Henry, J.D., Von Hippel, W. (2008). Empathy and social functioning in late adulthood. *Aging and Mental Health*, *12*(4), 499–503.

Baron-Cohen, S., Wheelwright, S. (2004). The empathy quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. *Journal of Autism and Developmental Disorder*, *34*(2), 163–75.

Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, *34*(4), 537–41.

Biswal, B.B., Mennes, M., Zuo, X.N., et al. (2010). Toward discovery science of human brain function. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(10), 4734–9.

Blair, R.J. (2005). Responding to the emotions of others: dissociating forms of empathy through the study of typical and psychiatric populations. *Consciousness and Cognition*, *14*(4), 698–718.

Blair, R.J., Peschardt, K.S., Budhani, S., Mitchell, D.G., Pine, D.S. (2006). The development of psychopathy. *Journal of Child Psychology and Psychiatry*, *47*(3–4), 262–76.

Buss, A.H., Perry, M. (1992). The aggression questionnaire. *Journal of Personality and Social Psychology*, *63*(3), 452–9.

Carr, L., Iacoboni, M., Dubeau, M.C., Mazziotta, J.C., Lenzi, G.L. (2003). Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(9), 5497–502.

Carrington, S.J., Bailey, A.J. (2009). Are there theory of mind regions in the brain? A review of the neuroimaging literature. *Human Brain Mapping*, *30*(8), 2313–35.

Cole, D.M., Smith, S.M., Beckmann, C.F. (2010). Advances and pitfalls in the analysis and interpretation of resting-state FMRI data. *Frontiers in Systems Neuroscience*, *4*, 8.

Constantino, J.N. (2002). *The Social Responsiveness Scale*. Los Angeles: Western Psychological Services.

Cox, C.L., Gotimer, K., Roy, A.K., Castellanos, F.X., Milham, M.P., Kelly, C. (2010). Your resting brain CAREs about your risky behavior. *PLoS One*, *5*(8), e12296.

Craig, A.D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Reviews Neuroscience*, *3*(8), 655–66.

Critchley, H.D. (2005). Neural mechanisms of autonomic, affective, and cognitive integration. *Journal of Comparative Neurology*, *493*(1), 154–66.

Davis, M.H. (1980). A multidimensional approach to individual differences in empathy. *JSAS Catalog of Selected Documents in Psychology*, *10*, 85.

Davis, M.H. (1983). Measuring individual-differences in empathy - evidence for a multidimensional approach. *Journal of Personality and Social Psychology*, *44*(1), 113–26.

Davis, M.H., Luce, C., Kraus, S.J. (1994). The heritability of characteristics associated with dispositional empathy. *Journal of Personality*, *62*(3), 369–91.

de Corte, K., Buysse, A., Verhofstadt, L.L., Roeyers, H., Ponnet, K., Davis, M.H. (2007). Measuring empathic tendencies: reliability and validity of the Dutch version of the interpersonal reactivity index. *Psychologica Belgica*, *47*(4), 235–60.

Decety, J. (2010). The neurodevelopment of empathy in humans. *Developmental Neuroscience*, *32*(4), 257–67.

Derogatis, L.R. (1994). *The Symptom Checklist-90-Revised*. Minneapolis: NCS Pearson, Inc.

Deutsch, F., Madle, R.A. (1975). Empathy: historic and current conceptualizations, measurement, and a cognitive theoretical perspective. *Human Development*, *18*(4), 267–87.

Di Martino, A., Shehzad, Z., Kelly, C., et al. (2009). Relationship between cingulo-insular functional connectivity and autistic traits in neurotypical adults. *American Journal of Psychiatry*, *166*(8), 891–9.

Dziobek, I., Rogers, K., Fleck, S., et al. (2008). Dissociation of cognitive and emotional empathy in adults with Asperger syndrome using the Multifaceted Empathy Test (MET). *Journal of Autism and Developmental Disorder*, *38*(3), 464–73.

Ebisch, S.J., Gallese, V., Willems, R.M., et al. (2011). Altered intrinsic functional connectivity of anterior and posterior insula regions in high-functioning participants with autism spectrum disorder. *Human Brain Mapping*, *32*, 1013–28.

Fan, Y., Duncan, N.W., de Greck, M., Northoff, G. (2011). Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. *Neuroscience and Biobehavioral Reviews*, *35*(3), 903–11.

Fox, M.D., Raichle, M.E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, *8*(9), 700–11.

Garrett, D.D., Kovacevic, N., McIntosh, A.R., Grady, C.L. (2010). Blood oxygen level-dependent signal variability is more than just noise. *Journal of Neuroscience*, *30*(14), 4914–21.

Gerschcovich, E.R., Cerquetti, D., Tenca, E., Leiguarda, R. (2010). The impact of bilateral cerebellar damage on theory of mind, empathy and decision making. *Neurocase*, *17*(3), 270–5.

Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(1), 253–8.

Han, Y., Wang, J., Zhao, Z., et al. (2011). Frequency-dependent changes in the amplitude of low-frequency fluctuations in amnestic mild cognitive impairment: a resting-state fMRI study. *Neuroimage*, *55*(1), 287–95.

Harari, H., Shamay-Tsoory, S.G., Ravid, M., Levkovitz, Y. (2010). Double dissociation between cognitive and affective empathy in borderline personality disorder. *Psychiatry Research*, *175*(3), 277–9.

Hooker, C.I., Verosky, S.C., Germine, L.T., Knight, R.T., D'Esposito, M. (2010). Neural activity during social signal perception correlates with self-reported empathy. *Brain Research*, *1308*, 100–13.

Hoptman, M.J., D'Angelo, D., Catalano, D., et al. (2010a). Amygdalofrontal functional disconnectivity and aggression in schizophrenia. *Schizophrenia Bulletin*, *36*(5), 1020–8.

Hoptman, M.J., Zuo, X.N., Butler, P.D., et al. (2010b). Amplitude of low-frequency oscillations in schizophrenia: a resting state fMRI study. *Schizophrenia Research*, *117*(1), 13–20.

Hurlemann, R., Patin, A., Onur, O.A., et al. (2010). Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. *Journal of Neuroscience*, *30*(14), 4999–5007.

Hynes, C.A., Baird, A.A., Grafton, S.T. (2006). Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. *Neuropsychologia*, *44*(3), 374–83.

Jenkinson, M., Bannister, P., Brady, M., Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*, *17*(2), 825–41.

Jones, A.P., Happe, F.G., Gilbert, F., Burnett, S., Viding, E. (2010). Feeling, caring, knowing: different types of empathy deficit in boys with psychopathic tendencies and autism spectrum disorder. *Journal of Child Psychology and Psychiatry*, *51*(11), 1188–97.

Kannurpatti, S.S., Biswal, B.B. (2008). Detection and scaling of task-induced fMRI-BOLD response using resting state fluctuations. *Neuroimage*, *40*(4), 1567–74.

Kelly, C., Zuo, X.N., Gotimer, K., et al. (2011). Reduced interhemispheric resting state functional connectivity in cocaine addiction. *Biological Psychiatry*, *69*(7), 684–92.

Kerem, E., Fishman, N., Josselson, R. (2001). The experience of empathy in everyday relationships: Cognitive and affective elements. *Journal of Social and Personal Relationships*, *18*(5), 709–29.

Keysers, C., Gazzola, V. (2007). Integrating simulation and theory of mind: from self to social cognition. *Trends in Cognitive Sciences*, *11*(5), 194–6.

Kunisato, Y., Okamoto, Y., Okada, G., et al. (2011a). Modulation of default-mode network activity by acute tryptophan depletion is associated with mood change: a resting state functional magnetic resonance imaging study. *Neuroscience Research*, *69*(2), 129–34.

Kunisato, Y., Okamoto, Y., Okada, G., et al. (2011b). Personality traits and the amplitude of spontaneous low-frequency oscillations during resting state. *Neuroscience Letters*, *492*(2), 109–13.

Kurth, F., Zilles, K., Fox, P.T., Laird, A.R., Eickhoff, S.B. (2010). A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Structure and Function*, *214*(5–6), 519–34.

Lawrence, E.J., Shaw, P., Baker, D., et al. (2007). Empathy and enduring depersonalization: the role of self-related processes. *Society for Neuroscience*, *2*(3–4), 292–306.

Lough, S., Kipps, C.M., Treise, C., Watson, P., Blair, J.R., Hodges, J.R. (2006). Social reasoning, emotion and empathy in frontotemporal dementia. *Neuropsychologia*, *44*(6), 950–8.

Lui, S., Li, T., Deng, W., et al. (2010). Short-term effects of antipsychotic treatment on cerebral function in drug-naive first-episode schizophrenia revealed by "resting state" functional magnetic resonance imaging. *Archives of General Psychiatry*, *67*(8), 783–92.

Mennes, M., Zuo, X.N., Kelly, C., et al. (2011). Linking inter-individual differences in neural activation and behavior to intrinsic brain dynamics. *Neuroimage*, *54*(4), 2950–9.

Miller, P.A., Eisenberg, N. (1988). The relation of empathy to aggressive and externalizing/antisocial behavior. *Psychological Bulletin*, *103*(3), 324–44.

Moriguchi, Y., Decety, J., Ohnishi, T., et al. (2007). Empathy and judging other's pain: an fMRI study of alexithymia. *Cerebral Cortex*, *17*(9), 2223–34.

Nummenmaa, L., Hirvonen, J., Parkkola, R., Hietanen, J.K. (2008). Is emotional contagion special? An fMRI study on neural systems for affective and cognitive empathy. *Neuroimage*, *43*(3), 571–80.

Patton, J.H., Stanford, M.S., Barratt, E.S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology*, *51*(6), 768–74.

Rankin, K.P., Gorno-Tempini, M.L., Allison, S.C., et al. (2006). Structural anatomy of empathy in neurodegenerative disease. *Brain*, *129*(Pt 11), 2945–56.

Reniers, R.L., Corcoran, R., Drake, R., Shryane, N.M., Vollm, B.A. (2011). The QCAE: a Questionnaire of Cognitive and Affective Empathy. *Journal of Personality Assessment*, *93*(1), 84–95.

Ritter, K., Dziobek, I., Preissler, S., et al. (2011). Lack of empathy in patients with narcissistic personality disorder. *Psychiatry Research*, *187*(1–2), 241–7.

Saxe, R. (2006). Uniquely human social cognition. *Current Opinion in Neurobiology*, *16*(2), 235–9.

Shamay-Tsoory, S., Harari, H., Szepsenwol, O., Levkovitz, Y. (2009a). Neuropsychological evidence of impaired cognitive empathy in euthymic

bipolar disorder. *Journal of Neuropsychiatry and Clinical Neurosciences*, *21*(1), 59–67.

Shamay-Tsoory, S.G. (2011). The neural bases for empathy. *Neuroscientist*, *17*(1), 18–24.

Shamay-Tsoory, S.G., Aharon-Peretz, J., Perry, D. (2009b). Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain*, *132*(Pt 3), 617–27.

Shamay-Tsoory, S.G., Harari, H., Aharon-Peretz, J., Levkovitz, Y. (2010). The role of the orbitofrontal cortex in affective theory of mind deficits in criminal offenders with psychopathic tendencies. *Cortex*, *46*(5), 668–77.

Shamay-Tsoory, S.G., Shur, S., Barcai-Goodman, L., Medlovich, S., Harari, H., Levkovitz, Y. (2007). Dissociation of cognitive from affective components of theory of mind in schizophrenia. *Psychiatry Research*, *149*(1–3), 11–23.

Shane, M.S., Stevens, M.C., Harenski, C.L., Kiehl, K.A. (2009). Double dissociation between perspective-taking and empathic-concern as predictors of hemodynamic response to another's mistakes. *Social Cognitive and Affective Neuroscience*, *4*(2), 111–8.

Shehzad, Z., Kelly, A.M., Reiss, P.T., et al. (2009). The resting brain: unconstrained yet reliable. *Cerebral Cortex*, *19*(10), 2209–29.

Shur, S., Shamay-Tsoory, S.G., Levkovitz, Y. (2008). Integration of emotional and cognitive aspects of theory of mind in schizophrenia and its relation to prefrontal neurocognitive performance. *Cognitive Neuropsychiatry*, *13*(6), 472–90.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D. (2004). Empathy for pain involves the affective but not sensory components of pain. *Science*, *303*(5661), 1157–62.

Skuse, D.H., Gallagher, L. (2011). Genetic influences on social cognition. *Pediatric Research*, *69*(5, Pt 2), 85R–91R.

Smith, S.M., Fox, P.T., Miller, K.L., et al. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(31), 13040–5.

Toro, R., Fox, P.T., Paus, T. (2008). Functional coactivation map of the human brain. *Cerebral Cortex*, *18*(11), 2553–9.

Zaki, J., Weber, J., Bolger, N., Ochsner, K. (2009). The neural bases of empathic accuracy. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(27), 11382–7.

Zhang, S., Li, C.S. (2010). A neural measure of behavioral engagement: task-residual low-frequency blood oxygenation level-dependent activity in the precuneus. *Neuroimage*, *49*(2), 1911–8.

Zhou, J., Greicius, M.D., Gennatas, E.D., et al. (2010). Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain : A Journal of Neurology*, *133*(Pt 5), 1352–67.

Zou, Q.H., Zhu, C.Z., Yang, Y., et al. (2008). An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *Journal of Neuroscience Methods*, *172*(1), 137–41.

Zuo, X.N., Di Martino, A., Kelly, C., et al. (2010). The oscillating brain: complex and reliable. *Neuroimage*, *49*(2), 1432–45.